Resuscitation of Severe Thermal Injury with Hypertonic Saline Dextran: Effects on Peripheral and Visceral Edema in Sheep

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Background: **Edema of tissue not directly injured by heat is a common complication after resuscitation of burn shock. Hypertonic 7.5% NaCl 6% dextran (HSD) infusion reduces early fluid requirements in burn shock, but the effects of HSD on peripheral and visceral tissue edema are not well-defined.**

Methods: **We measured the microcirculatory absorptive pressures of burned and nonburned skin and tissue water content of skin and other tissues in anesthetized sheep after 70% to 85% total body surface area scald and resuscitation. Fluid infusion was initiated 30 minutes after injury using 10 mL/kg HSD (n = 11) or lactated Ringer's (LR) (n = 12), with infusion rates titrated to restore and maintain preburn oxygen delivery (Do_2). Thereafter, both groups received LR infusions as needed to maintain Do_2 until the study's end at 8 hours. Colloid osmotic pressure was measured in plasma, and combined interstitial colloid osmotic and hydrostatic pressures were measured in skin.**

Results: **Both treatments successfully restored Do_2, but fluid requirements were less with the HSD group than with the LR group (43 ± 19 mL/kg vs. 194 ± 38 mL/kg, respectively, $p < 0.05$). The peripheral and visceral tissue water contents at 8 hours postinjury until the end of the study in both burn groups were significantly higher than in nonburn controls. However, HSD-treated sheep had significantly less water content in the colon (↓ 28%), liver (↓ 9%), pancreas (↓ 55%), skeletal muscle (↓ 21%), and nonburned skin (↓ 12%) compared with LR-treated sheep ($p < 0.05$ for each). HSD-treated sheep maintained significantly higher (3 to 5 mm Hg) plasma colloid osmotic pressure than LR-treated sheep.**

Conclusion: **There were no observed differences in edema in burn skin between the two treatment groups. The early volume-sparing effect of HSD and reduction in tissue edema are likely attributed to an increased extracellular osmolarity and a better maintenance of the plasma oncotic pressure.**

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Severe thermal injury causes rapid sequestration of fluid into the burn wound, resulting in hypovolemic shock and burn edema. Although the initial circulatory shock of thermal injury may be restored with large volumes of isotonic fluid, tissue edema in both burned skin and nonburned soft tissue is a common clinical complication. Soft tissue edema has been linked to organ dysfunction.[1–3] However, such findings are unconvincing until a clinical means exists to reduce edema without reducing vascular volume or circulatory functions. Only then can the value of edema reduction be assessed.

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Fluid filtration (J_v) between the microvasculature and tissues is governed by the net imbalance of Starling forces:

$$(1) \quad J_v = K_f(P_c - P_i) - \sigma(\Pi_p - \Pi_i),$$

where K_f is the capillary filtration coefficient, P_c is capillary pressure, P_i is interstitial hydrostatic pressure, σ is the osmotic reflection coefficient for protein, Π_p is colloid osmotic pressure in the plasma, and Π_i is the colloid osmotic pressure in the interstitium. Edema develops over time when the rate of fluid filtration (J_v) exceeds lymph flow (J_L).

$$(2) \quad \text{Edema} = \int_0^t (J_v - J_L)dt$$

Thermal injury is a unique form of trauma in which most, if not all, of the Starling forces are altered to increase fluid filtration. Measurements of microvascular Starling forces in partial-thickness wounds show that the initial burn edema may be largely attributable to a rapid decrease in P_i.[4,5] Edema in nonburned skin occurs once fluid resuscitation begins and develops because of a fall in Π_p without a concomitant fall in Π_i.[5] Additionally, there is an increase in P_c.[6] Several studies have demonstrated a sustained increase in capillary permeability in the burned skin and a transient increase in tissues not directly burned.[6,7] The search continues for the optimal

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fluid resuscitation for burn shock. The ideal therapy would restore cardiovascular and metabolic deficits of burn shock, normalize alternated forces and permeabilities in the microcirculation, and prevent compromised organ function.

Experimental and clinical studies have shown that the initial infusion of small volumes of 7.5% NaCl 6% dextran 70 (HSD) effectively resuscitates hemorrhage and trauma.[8–10] An osmotic redistribution of cellular water into the vascular and interstitial spaces has been demonstrated after hypertonic saline infusions in animals and humans and is the predominant physiologic mechanism for the volume-sparing effects of hypertonic and hyperoncotic solutions in hemorrhage.[11–13] However, fluid resuscitation of thermal injury is a greater challenge than treatment of hemorrhage, because burn resuscitation requires correction of both initial and sustained fluid losses attributable to the continued transcapillary extravasation known to occur for 6 to 24 hours after burn.[14]

There is controversy concerning the efficacy of colloid solutions in treating burn shock. It has been suggested that colloid solutions infused during a concurrent capillary leak result in interstitial trapping and sustained secondary edema.[15] On the other hand, some prestigious burn centers have advocated early use of colloids.[16] The effects of HSD treatment on edema in burn wounds and nonburned tissue early in the time course are not known.

Experimental studies of HSD treatment in thermal injury have produced mixed outcomes that depend on several factors, including total infused volume, infusion rate, solute concentration, and onset and period of HSD infusion. In general, the rapid 2-minute bolus infusion of HSD shown to be effective for hemorrhage may offer only transient benefits in burn resuscitation, whereas slower titrated infusions can significantly lower volume requirements during early resuscitation.[17–20] In one study, sheep subjected to an 85% total body surface area (TBSA) scald and initially resuscitated with 10 mL/kg HSD had a 74% reduction in net fluid balance compared with lactated Ringer's (LR).[18] In the present study, we measured Starling tissue forces and tissue edema in partial-thickness burned skin and nonburned skin in 12 sheep initially resuscitated with 10 mL/kg HSD followed by LR and 11 sheep resuscitated with LR only. Π_p, total interstitial absorptive pressures ($\Pi_I - P_i$), and tissue water content were measured during the first 8 hours of burn resuscitation.

MATERIALS AND METHODS

The study was approved by the University of Texas Medical Branch Animal Care and Use Committee. During the course of this experiment, we adhered to the Guidelines for the Care and Use of Experimental Animals established by the National Institutes of Health. Animals were fully anesthetized during the entire experimental protocol.

The present analysis was made from measurements in two separate series of experiments in which anesthetized adult female sheep (28–45 kg) were subjected to either a smaller, more severe 70% TBSA combined full thickness (30%) and partial-thickness (40%) burn[20] or a larger, less severe 85% TBSA partial-thickness burn.[18] In both series, animals were randomly assigned to one of two groups and resuscitated to the same endpoint using either 10 mL/kg LR or HSD as the initial test solution. The difference in surgical preparation, burn size, and burn severity did not result in any consistently significant differences in variables measured. In fact, the 70% and 85% TBSA scald groups exhibited responses in systemic variables that were virtually indistinguishable from each other, and data from both series were combined for the present analysis.

Animal Preparation

Sheep in the 85% TBSA scald series, treated with HSD ($n = 5$) or LR ($n = 6$) protocol, were subjected to an aseptic surgery 1 week before each experiment for placement of Swan-Ganz (Baxter Healthcare, Chicago, IL), arterial and venous catheters. Animals were allowed to recover and placed in individual cages with free access to food and water. Animals in the 70% TBSA scald series, treated with HSD ($n = 6$) or LR ($n = 6$), were instrumented the day of the study with Swan-Ganz and venous and arterial catheters. On the day of experiment, animals were anesthetized with isoflurane by mask and then orotracheally intubated, connected to a volume ventilator with anesthesia maintained throughout the experiment using 1% to 2% isoflurane in oxygen and adjusted as needed. Normocapnia was maintained by adjusting tidal volume and respiratory rate. After induction of anesthesia, each sheep had its wool shorn closely with clippers. Vascular catheters were connected to pressure transducers for monitoring. A Foley catheter was placed in the bladder for measurement of urine output.

Experimental Protocol

At least 1 hour was allowed to achieve a stable baseline period and record preburn measurements. TBSA was calculated for each sheep using a formula based on body weight, and then burn areas were measured with a ruler and outlined with a marker. The 85% TBSA partial-thickness scald was produced with a single application of 85°C water poured over the animal's entire body surface, sparing the head and lower limbs. A partial-thickness burn was evident by its erythematous appearance, which blanched upon light pressure. The time required to produce thermal injury was approximately 8 to 12 minutes. After scald, each sheep was placed in the prone position. Animals subjected to a 70% TBSA scald were initially placed in the prone position, and the full-thickness lesion was then made with several applications of 95°C water poured over the animal's hindquarter, back, and rear flanks (≈30% TBSA burn). The water was then cooled to 85°C, and one application was poured on the back and flanks of the thorax to produce a partial-thickness scald (≈40% TBSA burn). A 20×20 cm^2 area of the right flank was not scalded and served as a sampling site for nonburned skin.

Fluid resuscitation was started 30 minutes after thermal injury using a test solution of 10 mL/kg LR or HSD. Test solutions were placed in coded bags so that the investigator who burned the animals and conducted the experiments was blinded to the treatment. Infusion rate and volume were manually adjusted every 30 minutes using the intravenous drip chamber. The rate was titrated to restore and maintain baseline oxygen delivery (Do_2). Do_2 (mL O_2/min) was calculated using

$$Do_2 = CO \times (Hct/3 \times Sao_2 \times 1.39 + Pao_2 \times 0.003) \times 10, \quad (3)$$

where CO is cardiac output (L/min), Hct is hematocrit, Sao_2 is arterial hemoglobin saturation (%), and Pao_2 is oxygen tension (mm Hg). During the experiment baseline, Do_2 was achieved, adjusting infusion to achieve on-line target cardiac output (CO_{target}) that was calculated and set every 30 minutes.

$$CO_{target} = CO_{baseline} \times Hct_{baseline}/Hct_{at\ current\ time\ point} \quad (4)$$

Once the entire 10-mL/kg test solution was infused, infusion was continued in all sheep with LR to maintain Do_2 for the remainder of the 8 hours. At 8 hours, euthanasia was performed by intravenous injection of 20 mL saturated KCl.

Measurements

Vascular pressures in the aorta (mean arterial pressure [MAP]) and right atria (central venous pressure) and pulmonary artery pressure (PAP) and pulmonary artery occlusive pressure (PAOP) were measured every 30 minutes. Cardiac output was measured using the thermodilution technique and a cardiac output computer. Arterial blood gases and hematocrit were measured every 30 minutes using a blood gas analyzer and hematocrit centrifuge. Plasma was separated by centrifugation and stored at 4°C for later measurement of Π_p. Infused volume, urine volume, and hemodynamic measurements were made every 30 to 60 minutes after scald. Net fluid balance was calculated as the difference between infused volume and urine output. Plasma samples and biopsies of burned (partial-thickness only) and nonburned skin were taken at baseline, 30, 60, 120, 240, 360, and 480 minutes after scald.

Total interstitial absorptive pressure, which represents net pressure from two interstitial Starling forces (P_i) and (Π_i), was measured using a specially constructed tissue oncometer.[21]

$$\text{Total interstitial absorptive pressure} = \Pi_I - P_i \quad (5)$$

The measuring apparatus consists of a Gould p23db pressure transducer fitted to a saline-filled plexiglas chamber connected to a sample well covered with a semipermeable PM30 membrane that restricts entry of macromolecules with molecular weight greater than 30,000 Daltons (Amicon, Lexington, MA). The tissue oncometer measures net imbibition pressure or interstitial absorptive pressure generated by the interstitial hydrostatic (P_i) and interstitial osmotic pressure.

The minus sign reflects that a negative hydrostatic pressure acts in the same direction as a positive interstitial colloid osmotic pressure. Samples of dermis and plasma were placed directly on the membrane. The tissue oncometer was calibrated with a mercury manometer, and a 5% albumin solution was used as a control to check the membrane's integrity. Biopsies 1 cm^2 in size were removed from the left upper flank (burned skin) and right upper flank (nonburned skin). Skin biopsies were punched out, creating circular disks 8 mm in diameter. Samples were placed dermis side down on the oncometer and measured until osmotic pressure readings stabilized on the recorder, usually within 5 to 10 minutes. Plasma samples taken at the same time point were measured similarly. The membrane was rinsed with saline between measurements.

The isogravimetric capillary pressure (Pci), which is the capillary pressure for which neither filtration nor absorption occurs, was calculated using the measured Starling pressures:

$$Pci = P_i + (\Pi_p - \Pi_i).^{22} \quad (6)$$

This formula assumes $\sigma = 1$.

Skin biopsies (1–2 g) taken during the experiment and samples of liver, pancreas, skeletal muscle, ileum, colon, and kidney taken promptly after euthanasia were placed in previously weighed glass test tubes and immediately covered with parafilm to prevent water evaporation. Samples were weighed to the nearest 0.1 mg for total tissue wet weight and placed in a drying oven at 90°C and reweighed after 14 days, when the tissue had reached a final dry weight.

$$\text{Tissue water content} = [\text{wet wt (g)} - \text{dry wt (g)}]/\text{dry wt (g)} \quad (7)$$

Tissue taken from a group of noninjured animals (n = 9) served as a control for tissue water content.

Statistics

The data for both burn groups were combined after determining that there were no significant or apparent differences between the burn protocols with respect to fluid balance, hemodynamics, water content, or interstitial Starling forces. Results are reported as mean ± SEM. Each variable was analyzed from an analysis of variance for a two-factor experiment, with repeated measures on one factor (time), SAS/PRO (SAS Institute, Cary, NC). Fisher's least significant difference procedure is used for multiple comparisons of least square means with Bonferroni adjustment for the number of comparisons. Differences in tissue samples collected postmortem were determined with unpaired Student's *t* test. Statistical significance was set at $p < 0.05$.

Table 1 **Mean Cardiac Output, Mean Aortic Pressure, Pulmonary Artery Pressure, Central Venous Pressure, Pulmonary Artery Occlusion Pressure, and Hematocrit (mm Hg)**

		Baseline	Minutes Postburn					
			30	60	120	240	360	480
CO (L/min)	LR	4.4 ± 0.3	2.6 ± 0.2[a]	3.5 ± 0.3	3.9 ± 0.2	3.9 ± 0.2	4.0 ± 0.3	3.8 ± 0.2
	HSD	4.3 ± 0.4	2.3 ± 0.2[b]	4.1 ± 0.3	3.8 ± 0.3	4.2 ± 0.3	4.0 ± 0.3	4.0 ± 0.4
MAP	LR	96 ± 4.7	71 ± 5.1[a]	84 ± 3.2[a]	79 ± 3.8[a]	86 ± 2.8[a]	76 ± 3.1[a]	78 ± 5.9[a]
	HSD	104 ± 4.7	72 ± 3.8[b]	92 ± 7.1	89 ± 4.5[b]	86 ± 5.5[b]	78 ± 4.2[b]	80 ± 3.9[b]
PAP	LR	15 ± 1.1	18 ± 1.5	20 ± 1.3[a]	21 ± 1.6[a]	24 ± 2.3[a]	22 ± 1.3[a]	24 ± 2.6[a]
	HSD	17 ± 0.6	17 ± 1.1	19 ± 0.9	18 ± 1.3	18 ± 1.4	17 ± 1.3	18 ± 1.1
CVP	LR	0.3 ± 0.4	1.0 ± 0.6	1.6 ± 0.6[a]	2.3 ± 0.9[a]	3.2 ± 1.0[a]	3.1 ± 0.7[a]	4.7 ± 1.0[a]
	HSD	0.6 ± 0.5	1.8 ± 0.6	2.0 ± 0.6[b]	1.8 ± 0.5[b]	3.0 ± 0.7[b]	3.3 ± 0.8[b]	3.9 ± 0.8[b]
PAOP	LR	7.3 ± 0.9	11.0 ± 0.9[a]	11.1 ± 1.0[a]	11.5 ± 1.4[a]	12.7 ± 1.5[a]	12.1 ± 1.0[a]	14.0 ± 2.1[a]
	HSD	8.5 ± 0.6	10.8 ± 1.0	10.7 ± 0.7	12.0 ± 0.9[b]	9.0 ± 0.8[c]	9.9 ± 0.8[c]	11.5 ± 0.8[b]
Hct (%)	LR	25.0 ± 2.0	31.0 ± 2.0[a]	29.0 ± 2.0	28.0 ± 2.0	29.0 ± 2.0	30.0 ± 2.0	28.0 ± 3.0
	HSD	26.0 ± 1.0	30.0 ± 2.0[b]	30.0 ± 2.0	29.0 ± 2.0	30.0 ± 2.0	32.0 ± 3.0	30.0 ± 2.0

Data are mean ± SEM for 12 animals resuscitated with LR only and 11 animals resuscitated with 10 mL/Kg HSD initially and then by LR. [a] $p < 0.05$ LR vs. baseline; [b] $p < 0.05$ HSD vs. baseline; [c] $p < 0.05$, HSD vs. LR.

RESULTS

Hemodynamics

At the end of the first 30 minutes after scald injury, CO decreased by 30% and 40%, oxygen delivery decreased by 30%, and MAP decreased by 30% to 35% in both groups before the initiation of resuscitation (Table 1, Fig. 2). Fluid resuscitation restored CO to near-baseline values in both groups. Both HSD and LR infusions raised MAP, but MAP continued to remain 10% to 20% below baseline in both groups.

Right and left atrial filling pressures as measured by central venous pressure and PAOP from the Swan Ganz catheter were elevated 3 to 6 mm Hg after burn and during resuscitation (Table 1). However, HSD-treated animals had PAOPs that were 2 to 6 mm Hg lower ($p < 0.05$) between 4 to 8 hours postburn compared with the LR-treated group. Mean PAP remained unchanged after HSD resuscitation, whereas PAP increased 5 to 9 mm Hg from baseline in the LR group throughout the resuscitation period. However, this difference between groups was not statistically significant.

Thermal injury resulted in a 30% decrease in the calculated oxygen delivery before the initiation of resuscitation (Fig. 1). Titration of rate and volume of fluid delivery restored and maintained oxygen delivery at preinjury values throughout the experimental period. Maintenance of baseline oxygen delivery was associated with a slight decrease in cardiac output compared with baseline and a prolonged significant but small increase in hematocrit (hemoconcentration) after thermal injury.

Fluid Balance

Table 2 summarizes the cumulative volumes of fluid input and urine output after resuscitation in LR and HSD groups. At the end of the 8-hour experiment period, resuscitation volume infused with the LR group required approximately four times more fluid than with the HSD group to maintain baseline oxygen delivery. Urine output at each time period was not significantly different between groups. The calculated cumulative net fluid balance (volume infused minus urine out) per kilogram of body weight was nearly five times more than with the HSD group (Table 2).

Plasma Sodium Concentration

Plasma sodium concentrations increased from 140 ± 1.0 to 146 ± 2.4 mEq/L during the first 30 minutes of resuscitation with HSD and reached a maximum of 153 ± 3.2 mEq/L at 4 hours postinjury. In the LR group, plasma sodium continued to decline throughout the experiment to 130 ± 1.7 mEq/L at the end of 8 hours (Fig. 2).

Plasma Oncotic Pressure

There was no change in Π_p in the first 30 minutes after burn. After resuscitation, Πp decreased in both groups, from 21 mm Hg at baseline to 12 mm Hg in the HSD group and about 8 mm Hg in the LR group (Fig. 3). At all time points after fluid infusion, colloid osmotic pressure was about 5 mm Hg higher in the HSD group than in the LR group.

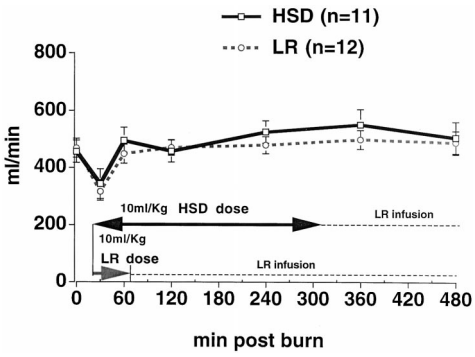

Fig. 1. *Oxygen deliver (Do_2) calculated every 30 minutes in burn-injured sheep treated with LR or HSD and followed by LR in both groups. Infusion rates were adjusted to restore and maintain baseline Do_2. Data are mean ± SEM.*

Table 2 Cumulative Volume Infused, Urine Output, and Net Volume

		Baseline	Minutes Postburn					
			30	60	120	240	360	480
Vol (mL/kg)	LR	—	—	14 ± 2	44 ± 5	102 ± 13	159 ± 21	221 ± 27
	HSD	—	—	2 ± 1[a]	4 ± 1[a]	13 ± 4[a]	33 ± 9[a]	59 ± 14[a]
Urine (mL/kg)	LR	—	2 ± 1	3 ± 1	4 ± 1	6 ± 2	14 ± 6	22 ± 10
	HSD	—	1 ± 1	2 ± 1	3 ± 1	8 ± 2	12 ± 3	17 ± 4
Net vol (mL/kg)	LR	—	−2 ± 1	11 ± 2	41 ± 5	96 ± 13	145 ± 19	198 ± 25
	HSD	—	−1 ± 1	−1 ± 1[a]	1 ± 1[a]	4 ± 3[a]	20 ± 11[a]	43 ± 12[a]

Data are mean ± SEM for 12 animals resuscitated with LR only and 11 animals resuscitated with 10 mL/Kg HSD initially and then by LR.
[a] $p < 0.05$, HSD vs. LR.

Total Interstitial Absorptive Pressure

There was no significant change in the total interstitial absorptive pressure 30 minutes after burn and before fluid infusion for both the partial-thickness burned skin and the nonburned skin (Fig. 4). However, 30 minutes after the start of infusion, there was an apparent increase in mean $[\Pi_i - P_i]$ in the HSD group, whereas the mean $[\Pi_i - P_i]$ in the LR group decreased. Thereafter, the $[\Pi_i - P_i]$ decreased in both the burned and nonburned skin for both treatment groups throughout the 8-hour experiment, although the decline tended to be less in the HSD group. In nonburned skin, there was a significant difference between groups at three time points, whereas in burned skin, there was a significant difference at only one time point (Fig. 4).

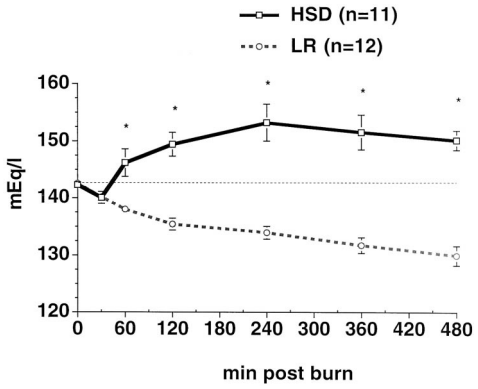

Fig. 2. *Plasma sodium in burn-injured sheep treated with LR or HSD followed by LR in both groups. Infusion rates were adjusted to restore and maintain baseline Do_2. Data are mean ± SEM.* Asterisk *indicates* $p < 0.05$, *HSD (7.5% NaCl/6% dextran 70) versus LR.*

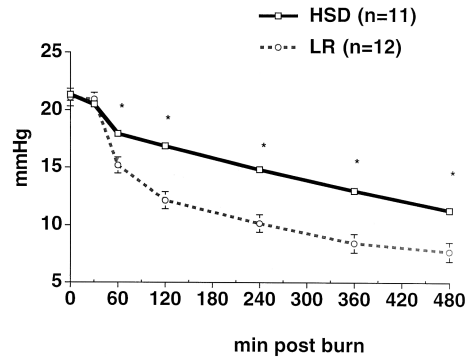

Fig. 3. *Plasma colloid osmotic pressure (*Πp*) in burn-injured sheep treated with LR or HSD followed by LR in both groups. Infusion rates were adjusted to restore and maintain baseline Do_2. Data are mean ± SEM.* Asterisk *indicates* $p < 0.05$, *HSD (7.5% NaCl/6% dextran 70) versus LR.*

Isogravimetric Capillary Pressure

Before thermal injury, the mean Pci was 5 to 6 mm Hg for both groups. Burn did not cause a significant reduction in Pci, but once resuscitation was initiated, there was a rapid decrease in the Pci in both the LR and HSD groups. Sixty minutes postburn, the Pci in burned skin had declined to negative values (−2 to −3 mm Hg) in the LR group but remained positive in the HSD group (Fig. 5). Similar changes

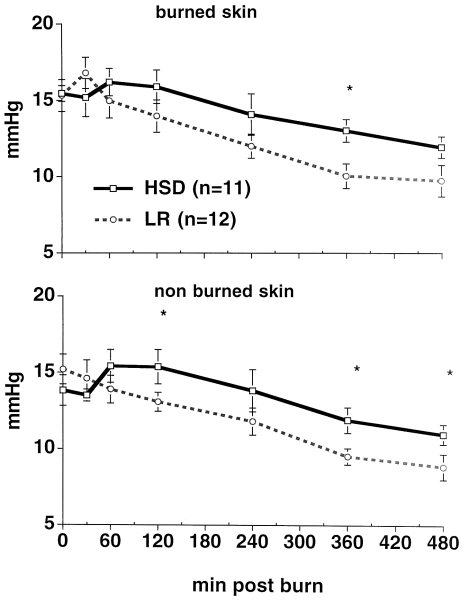

Fig. 4. *Total interstitial absorptive pressure (*$\Pi_I - P_i$*) measured on tissue oncometer. Burned and nonburned skin samples were placed on semipermeable membrane restrictive to macromolecules greater than 30,000 Kd. Measurements made on skin sampled before and after burn injury and during resuscitation.* Asterisk *indicates* $p < 0.05$, *HSD (7.5% NaCl/6% dextran 70) versus LR.*

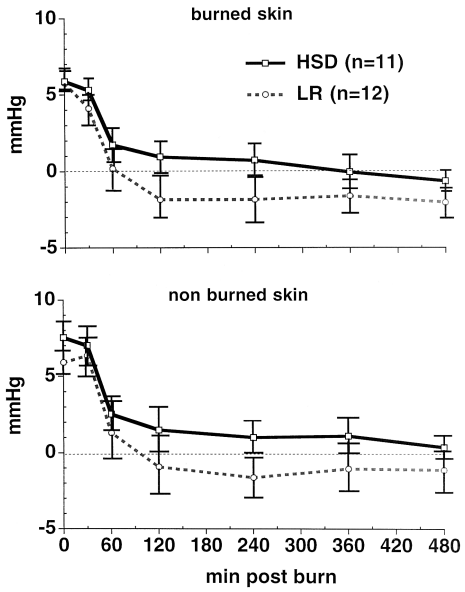

Fig. 5. *Isogravimetric capillary pressure: Pci = P_I − (Π_p − Π_i). Pci calculated as effective sum of other Starling pressures for burned and nonburned dermis. Measurements were made before and after burn injury and during resuscitation. Data are mean ± SEM.* Asterisk *indicates* p < *0.05, HSD (7.5% NaCl/6% dextran 70) versus LR.*

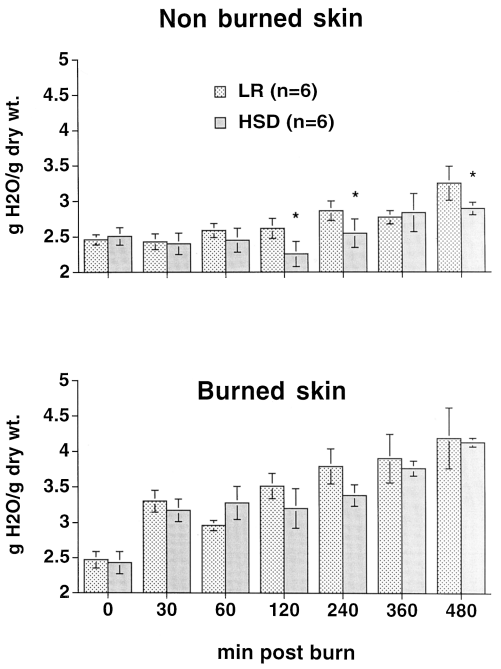

Fig. 6. *Water content in burn and nonburned dermis. Measurements were made before and after burn injury and during resuscitation. Data are mean ± SEM.* Asterisk *indicates* p < *0.05, HSD (7.5% NaCl/6% dextran 70) versus LR.*

in Pci were observed in nonburned skin, although the declines were slightly less than in burned skin at the end of the 8-hour experiment period.

Skin Edema

Water content of partial-thickness burned skin increased 30% to 40% in the first 30 minutes after thermal injury alone (Fig. 6). LR resuscitation resulted in a steady increase in water content, reaching 70% above baseline by 480 minutes (Fig. 6). Although the water content of burned skin in the HSD groups was similar to the LR group at the end of the 8-hour experiments, a steady rise was less apparent during the HSD infusion. Mean water content in nonburned skin was slightly less than baseline at 30 minutes after burn but increased steadily after LR resuscitation. On the other hand, HSD treatment resulted in no apparent edema in nonburned skin at 120 and 240 minutes postburn (Fig. 6). At 120, 240, and 480 minutes, the water content of nonburned skin in the HSD group was increased above baseline but was significantly less than in the LR group.

Soft Tissue Edema

Water content was measured in samples taken after euthanasia or 8 hours postinjury. LR infusions resulted in edema or a significant (10% to 55%) increase in water content of the colon, kidney, liver, skeletal muscle, and pancreas compared with tissues from the control nonburned animals. There were significant increases in water content in the kidney, liver, and pancreas at 8 hours postburn in the HSD group. However, this increased water content was of a lesser magnitude when compared with LR. HSD significantly reduced edema in the liver and pancreas and seemed to prevent edema in the colon and skeletal muscle of animals with thermal injury (Fig. 7).

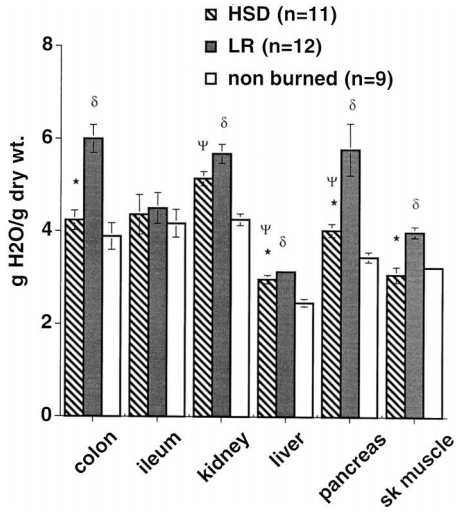

Fig. 7. *Tissue water content for colon, ileum, kidney, liver, pancreas, and skeletal muscle. Measurements made on samples taken after euthanasia. Data are mean ± SEM from 9 to 12 animals per group.* Asterisk *indicates* p < *0.05, HSD (7.5% NaCl/6% dextran 70) versus LR;* ψ, p < *0.05, HSD vs nonburned skin;* δ, p < *0.05, LR vs nonburned skin.*

DISCUSSION

The most common resuscitation regimen for treating thermal injury in the United States is infusion of LR using 0.25 mL/kg/% TBSA burn, the initial rate set by the Parkland formula. The Parkland formula provides an estimate of fluid requirements for the first 24 hours with half of the fluid administered in the first 8 hours and the other half over the next 16 hours. In practice, after setting the initial Parkland rate, fluid infusion rates are adjusted as needed to maintain a urine output between 0.5 to 1 mL/kg/h. Actual fluid volume administration often exceeds the Parkland estimates, and net accumulations of 10 to 20 liters in the first 24 hours are not uncommon after burns in adults. Such resuscitations result in a substantial observable edema in the burn wound as well as alteration in electrolytes and dilution in plasma protein balances, which contribute to both extracellular and intracellular edema in nonburned tissues.[14] Although peripheral edema is rarely life threatening, soft tissue organ edema has been associated with delayed healing, sepsis, and paralytic ileus.[2,3]

Several experimental burn resuscitation studies using hypertonic saline and hypertonic saline dextran have suggested that such solutions can reduce the early fluid requirement while maintaining stable hemodynamics.[18] However, there is little data on fluid balance in specific tissues.

The present study was undertaken to evaluate the changes in water content in specific tissues and provide data on the mechanisms of the early volume-sparring effect of HSD in large thermal injury. We compared the initial resuscitation using 10 mL/kg HSD or LR beginning 30 minutes after thermal injury titrated with the endpoint of baseline Do_2. Do_2 was chosen as the endpoint of resuscitation over urine output or other hemodynamic variables, because the natriuretic, diuretic, and vasodilator effects of hypertonic and hyperoncotic solutions could confound the use of urine output and arterial blood pressure as endpoints.

Thermal injury resulted in an initial 20% to 30% decrease in Do_2, which was associated with a 30% to 40% decrease in CO and a 10% to 20% increase in hematocrit. Reduced CO coupled with hemoconcentration indicates the expected contracted plasma volume and initial development of circulatory shock. After thermal injury but before resuscitation, there were slight elevations in right and left atrial pressures with a decreased CO, whereas after resuscitation, filling pressure elevations were increased above baseline and cardiac outputs were slightly reduced below baseline. These data are suggestive of impaired cardiac performance and are consistent with previous reports of myocardial depression observed after thermal injury.[23]

Studies by Horton et al.[24,25] and Elgjo et al.[26] show that early HSD infusion can protect against myocardial depression measured 24 hours after thermal injury in animals in which only LR is used for treatment. In the present study, HSD treatment resulted in slightly lower left heart filling pressures beginning 4 hours after resuscitation and an equal or higher CO compared with the LR treatment. The decreased filling pressures with HSD resuscitation may reduce capillary pressure, one of the mechanisms of edema formation. Finally, the significantly higher PAP in the LR group compared with the HSD group could indicate some degree of impaired left ventricular performance. The ability of hypertonic saline to lower filling and pulmonary pressures when shock resuscitation is titrated to a physiologic endpoint has also been reported in hemorrhaged sheep and swine.[8,27,28]

Both resuscitation regimens effectively restored and maintained Do_2 and returned other cardiovascular parameters to near-normal levels. Most significant is that HSD achieved this resuscitation with 78% less volume during the 8-hour experiment. This is notably different than our earlier study using a similar model in which a 4-mL/kg dose of HSD was infused as a 2-minute bolus and the volume-sparing effect lasted less than 2 hours. Rapid infusion of HSD after thermal injury may have resulted in overresuscitation and overperfusion of thermal injured tissues, aggravating edema.[17] The HSD volume-sparing effect in the present study may have resulted from titrating the infusion to a specific physiologic endpoint (Do_2). The 10-mL/kg HSD dose in the present study was titrated to restore and maintain Do_2, resulting in a fairly steady infusion rate of 2 mL/kg/h, with little deviation of this rate during the initial 4 to 6 hours. On the other hand, rebounds of fluid requirements have occurred after early volume sparing in 24-hour studies of resuscitation using HSD for treatment of a 40% TBSA burn in conscious sheep.[29]

The slow infusion of HSD caused only mild hypernatremia, as peak plasma sodiums were less than 155 mEq/L in the HSD group. The 10-mL/kg dose of HSD, infused slowly, increased plasma sodium to the same levels seen in trauma patients as well as experimental animals administered a bolus infusion of a smaller 4-mL/kg dose of HSD.[9,10] The hypernatremia and associated hyperosmolarity are responsible for the osmotic mobilization of cellular water and are likely mechanisms for the reduced edema seen in nonburned tissues. No untoward effects of this level of sodium have been reported in trauma patients treated with HSD.[30] Interestingly, LR resuscitation was associated with changes in plasma sodium of similar magnitude, but in the opposite direction. The reduction in plasma sodium to 130 mEq/L or less in the LR group cannot be fully explained by the 130-mEq/L sodium concentration of LR, because this would require the entire extracellular space to be replaced with LR solution. Rather, it suggests either greater retention of free water by the kidney or loss of sodium out of the vascular compartment. Monofo et al.[31] showed increased sodium in skeletal muscle after burn, and Baxter[1] reported increased cellular sodium content in muscle associated with partial membrane depolarization. Cellular edema and membrane depolarization are also reported after hemorrhagic and septic shock.[32–35] We previously reported that hypertonic saline resuscitation normalized cellular sodium and membrane potential after hemorrhagic shock whereas isotonic resuscitation did not.[32]

The reduction in Π_p in both groups results from both the dilution effects of volume expansion and the loss of vascular protein attributable to increased capillary permeability. The lesser decrease in Π_p observed in the HSD group at all resuscitation time points is likely attributable to the oncotic properties of dextran, because HSD has been shown not to affect capillary permeability.[36] A higher colloid osmotic pressure in plasma translates into a greater retention of fluid within the capillary and is a likely mechanism for the reduced edema we found in several nonburned tissues in HSD-treated animals. A contributing factor for the edema could be the higher capillary pressures, which is consistent with the generally higher venous and filling pressures of the LR-treated animals.

P_i is slightly negative in normal dermis, about –1 to –2 mm Hg, whereas the interstitial colloid osmotic pressure is 10 to 15 mm Hg.[37] Combined, these pressures exert a net 8 to 14 mm Hg of absorptive pressure across the capillary wall. Interestingly, in the present study, the Π_i-P_i had changed very little at 30 minute postburn and before fluid resuscitation despite a 30% increase in water content in burn wound. Lund and colleagues[4,38] showed that large negative P_i are generated in burned dermis immediately postburn and may be the predominant mechanism for rapid edema formation of the burn wound. Lund and colleagues[4,38] also reported that as edema forms, this absorptive or imbibition pressure is mostly relieved, and interstitial P_i returns to a slightly subatmospheric pressure or even becomes positive with resuscitation. We previously reported[5] that a sustained slightly negative P_i remains in burned skin even after large volumes of LR are given. Increased interstitial volume with reduced interstitial pressure is by definition an increase in interstitial compliance and may be a mechanism that sustains burn wound edema.[5] P_i measurements in nonburned skin have shown that P_i becomes positive within 30 minutes of fluid resuscitation, suggesting normal compliance in nonburned skin.[4,5]

Although capillary permeability is undoubtedly increased in the burn wound, Π_i may only increase slightly or not at all, as studies of lymph from the burn wound and directly sampled interstitial fluid indicate protein sieving still occurs in the burned dermis.[7,39] Our data is consistent with these and other reports of changes in interstitial absorptive pressure. The interstitial absorptive pressures of nonburned skin in HSD-treated sheep initially increased and remained higher than in LR-treated sheep. This is likely attributable to the HSD mobilization of interstitial water from nonburned tissues and the subsequent concentration of interstitial protein and increasing Π_i. The absence of edema in nonburned skin during HSD infusion supports this theory. A similar trend of changes in interstitial absorptive pressure after HSD treatment was observed in burned skin, but the difference was only significant at one time point. Because edema in the burned skin was not reduced at all with HSD, the higher Π_i-P_i in burned skin likely reflects capillary filtration of fluid with a higher oncotic pressure in the plasma. One limitation in this study is that we could not separate the P_i from the Π_i with four measurements. However, calculation of the Pci provided a measure of net changes in the effective plasma to interstitial fluid driving forces.

The Pci represents the pressure in the capillary, which would result in fluid equilibrium or the capillary pressure where filtration and absorption forces are exactly balanced. Thus, a capillary pressure below Pci results in a net capillary absorption of interstitial fluid, whereas capillary pressures greater than Pci causes a net capillary filtration. Before thermal injury, Pci was 6 to 8 mm Hg. Pci was substantially reduced at 1 hour (after 30 minutes of resuscitation) from its baseline level and actually became negative at 120 minutes after injury in the LR group. This suggests that capillary reabsorption of fluid cannot occur in either burned or nonburned skin, because capillary pressure cannot be less than zero. At this point, lymphatic clearance is the only mechanism by which burn edema can be cleared. Altered Starling forces contribute to sustaining edema in the skin and possibly other tissues. Pitkanen et al.[40] used wicks to sample interstitial fluid in burn patients and showed that LR resuscitation resulted in a reversal in the normal plasma-interstitial oncotic gradient. These authors concluded that the large decrease in Π_p was primarily responsible for the reversed oncotic gradient. Likewise, the large fall in Π_p that we found with the LR group is likely the predominant factor that causes Pci to become negative.

The overall volume-sparing effect of HSD in the present study translated into less tissue edema in the liver, pancreas, and nonburned skin and completely eliminated edema in the colon and skeletal muscle. Reductions in visceral and organ edema after HSD treatment may provide significant clinical benefit, because edema in these organs may be associated with impaired nutrient uptake from the gut and possibly greater risk of bacterial translocation.[41] Tokyay et al.[42] showed less bacterial translocation after HSD treatment of burn shock. The skeletal muscle edema observed in the present study is of particular interest. LR resuscitation increased skeletal muscle water content by 21%. This increase translates into 3 to 4 liters of volume for a 70-kg patient, assuming that muscle is 40% of body weight. Because skeletal muscle is 80% intracellular, this suggests substantial cellular swelling in skeletal muscle with LR resuscitation of burn shock. Skeletal and cardiac muscle cells have also been shown to partially depolarize after burn shock.[1] Similar results have been reported for hemorrhagic and septic shock.[33–35] In the present study, skeletal muscle water content in the HSD group was similar to nonburned controls. These data support the view that the volume-sparing effect of HSD is primarily attributable to mobilization of cellular water. Normalization of intracellular water content, electrolyte composition, and membrane potential has been reported after 7.5% NaCl treatment of hemorrhage.[32]

Despite theoretical suggestions that colloid resuscitation may increase burned skin edema by the deposition of dextran

into the extravascular space,[43] the present study suggests this does not occur in the first 8 hours with a 10-mL/kg dose of 6% dextran infused with hypertonic saline. However, the early volume-sparing effect of HSD and reduced edema can be overcome with subsequent infusions. Studies with an initial 30-minute 4-mL/kg bolus infusion of HSD resuscitation followed by LR resuscitation show that a rebound of total fluid needs can occur after 12 hours.[19]

It is important to consider any deleterious effects that HSD infusions may have on clinical outcome. We recently reviewed the clinical literature on the use of HSD for intraoperative volume support and the initial treatment of traumatic hypotension.[12,44] Clinical use of HSD was largely limited to fixed doses of 250 mL or about 4 mL/kg in adults. This is less than half the dose in the present study, although the smaller doses were generally infused as a 30-minute or faster bolus compared with the 2 to 4 hour infusions of the present study. Taken as a whole, these studies show this dose of HSD to be more effective at expanding volume, increasing blood pressure, and lowering fluid requirements compared with isotonic treatments. There are no reports of renal failure, central pontine myelinolysis, or death associated with HSD. Indeed, late complications and rates of organ failure in trauma trials were lower.[9] However, hypertonic resuscitation could clearly be deleterious if infused too rapidly, inducing volume overload, or if continuous infusions are maintained for excessive periods. Prien et al. reported acute volume overload and signs of cardiac ischemia in cardiac surgery patients when a 7.5% NaCl hetastarch formulation was infused at a fixed time period.[45] Subsequent studies suggest that the use of HS hetastarch is safe in cardiac patients with titrated infusions.[46] More to the point is a retrospective analysis of the sustained use of hypertonic acetate followed by infusions of 3% NaCl and lactate formulations over 12 to 48 hours in burn patients, which showed a higher incidence of both mortality and renal failure compared with clinical records of isotonic resuscitation.[47] It is difficult to compare the sustained use of hypertonic acetate and 3% NaCl with the present use of HSD in this study. However, others using similar 2% to 3% NaCl formulations with good clinical outcomes and decreased mean mortality suggest a limited serum sodium of 160 to 165 mEq.[48,49] It should be noted that fixed doses of HSD rarely cause elevations above 160 mEq, and serum sodium was at all times below this level in the present study.

In summary, initial resuscitation of large thermal injury using HSD followed by LR results in significantly less peripheral and visceral edema and substantially less volume needs when compared with LR resuscitation during the first 8 hours after burn resuscitation. The mechanisms of these volume-sparing and edema-preventing effects are most likely attributable to the mobilization of cellular and interstitial water caused by the combined actions of the hyperosmotic saline and the higher Π_p attributable to the infused dextran. Additionally, improved cardiac function in the HSD group may have also played a role. Long-term studies are needed to determine whether the early volume-sparing effect of HSD offers any clinically relevant and long-term benefits or risks for burn resuscitation.

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